UNITED STATES PATENT AND TRADEMARK OFFICE

C / C

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,751	06/01/2001	Seo Young Jeong	0217-0006	4257

23117 7590 10/17/2005

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,751	JEONG ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *2,4,14-21,31-39,41,43 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-13,22-30,40,42 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 January 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/1/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

500

DETAILED ACTION

This is the First Office Action on the Merits of the Application filed 1 June 2001 as the US National Stage of international stage of international application 09/744,751 filed 30 July 1999, which claims benefit of Korean patent application 1998-31249 filed 31 July 1998.

The claims originally filed in the instant case are presented as a copy of an Article 34 Amendment filed in the international application, which amendment contains claim numbers for canceled claims 3, 4, 7, 8, 26-51, 59, 73, 74, 77 and 78. As these claims were not pending in the instant case, the remaining claims have been renumbered in accordance with Rule 1.126, which requires that the claims presented in consecutive order. Therefore, claims 5, 6, 9-25, 52-58, 60-72, 79 and 80 have been renumbered 3, 4, 5-21, 22-28, 29-43, 44 and 45, respectively. All future submissions should be consistent with the renumbered claims. In addition, Applicant should amend the claims such that the claim dependency is consistent with the renumbering.

The preliminary amendments filed 29 January 2001 and 7 September 2005 have been entered.

Election/Restrictions

Applicant's election with traverse of Group I (renumbered claims 1, 3, 5-13, 22-30, 40, 42 and 44) in the reply filed on 7 September 2005 is acknowledged. The traversal is on the ground(s) that there has been no showing that examination of Groups I and II would constitute an undue burden. This is not found persuasive because the instant application is filed under 35 USC §371 and is therefore restricted based on Unity of Invention rules, which do not require a showing of undue burden. Furthermore, even if such a showing were required in the instant case,

restriction would still be proper. The instant Group I is limited to an oil-in-water emulsion comprising a non-triglyceride oil and the instant Group II is limited to a solid-lipid nanoparticle comprising fat of triglycerides. Each invention is limited to comprising distinct constituents and exhibits a distinct physical form. Clearly, examination of each group would require search and consideration of distinct art, and a determination that the subject matter of either Group is patentable over the art does not evidence patentability of the other Group. Therefore, examination of both Groups together in a single application constitutes a serious burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 2, 4, 14-21, 31-39, 41, 43 and 45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the 7 September reply.

Claims 1, 3, 5-13, 22-30, 40, 42 and 44 are under consideration.

Drawings

Figure 19 is objected to as being unclear. The drawing purports to show luciferase expression in nasal extract and lung. However, there is no difference in the bars representing the data from nasal extract and lung. Therefore, it is not possible to distinguish which bar represents which sample. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Specification

The disclosure is objected to because of the following informalities: The legends for Figures 10, 11, 13 and 20 do not match the brief description. Specifically, the legends indicate that the data are represented by various Greek letters which do not appear in the drawings. In addition, the brief description of Figure 12 states that the data presented show transfection

efficiency using "different lipid gene carriers" but neither the legend nor the drawing identify the lipid gene carriers used or indicate how they differed. The legend should be expanded to clarify the data shown. Finally, the brief description of Figure 8 refers to panels A and B with panel B being data for a DOTAP/DOPE squalene lipid emulsion. However, there is only one panel in Figure 8 and it appears to show data obtained for DOTAP/DOPE/diolein.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The claims are directed to an oil-in-water emulsion for delivering biologically active material, or a method for preparing an oil-in-water emulsion for delivering biologically active material selected from RNA, antisense nucleic acid, ribosome and oligonucleotide. There is no antecedent basis for the terms RNA, antisense nucleic acid, ribosome and oligonucleotide. The specification should be amended to provide proper antecedent basis for the terms, while being careful not to introduce new matter into the specification.

Appropriate correction is required.

Claim Objections

Claims 28 and 42 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 28 is directed to the complex of claim 22 wherein the complex is transferred by a particular route. The limitations recited in claim 28 are intended use limitations and, as the

complex of claim 22 can be delivered by any of those routes, the recitation of intended use does not further limit the claims from which claim 28 depend.

Claim 42 is directed to the method of claim 3, wherein the cationic lipid transfection agent is added in the oil phase instead of the aqueous phase. However, the method of claim 3 is limited to preparing an aqueous phase comprising one or more cationic lipid transfection agents. Therefore, a method wherein the cationic lipid transfection agent is added in the oil phase instead of the aqueous phase is not within the scope of claim 3.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5-13, 22-30, 40, 42 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for oil-in-water lipid emulsions for delivering various nucleic acid molecules, does not reasonably provide enablement for an oil-in-water emulsion for delivering a ribosome. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not

limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to an oil-in water lipid emulsion or a method of making an oil-in-water lipid emulsion, wherein the claims recite that the emulsion is to be used for delivering a ribosome (*i.e.*, a large multiprotein and RNA complex). Furthermore, although the claims do not recite where delivery is to take place, it is clear from the disclosure as a whole, that delivery includes delivery across the plasma membrane and into a cell. Still further, as ribosomes must have access to the interior of the cell in order to function, it is clear that useful delivery of a ribosome would require delivery across the plasma membrane. As the claims recite that the emulsion will be used to deliver a ribosome and useful delivery requires delivery into a cell, it is incumbent upon the specification to teach the skilled artisan how to make an emulsion that can be used to deliver a ribosome into a cell.

State of the prior art and level of predictability in the art: With regard to delivering large protein nucleic acid complexes such as ribosomes into cells, the art teaches delivery of many compounds across cell walls and membranes has proved more difficult than for the structurally homogeneous nucleic acid molecule. For example, in spite of tremendous interest in delivering peptides and proteins into cells, there have been very few molecules identified as capable of providing non-invasive delivery of peptides and proteins. Hawiger (1999) *Curr. Opin. Chem. Biol.* 3:89-94 teaches, "[t]he plasma membrane of eukaryotic cells is inherently impermeable to

peptides and proteins that lack specialized membrane receptors or transport proteins" (paragraph bridging pages 89-90) and "invasive techniques of microinjection or applications of membrane-disrupting pore-forming reagents...are usually employed to introduce antibodies, synthetic peptides or other non-cell membrane-permeable molecules into cells" (sentence bridging the left and right columns on page 89). Although Hawinger goes on to teach that a very limited number of peptide molecules have been identified as capable of facilitating intracellular delivery of some peptides and proteins (see especially Table 1), Veach *et al.* (2004) *J. Biol. Chem.* 279: 11425-11431 teaches that as of 2004 the mechanism by which these peptides translocate cargo across the plasma membrane remained unexplained (paragraph bridging the left and right columns on page 11425). Thus, the combined teachings of Hawinger and Veach *et al.* show that, even many years after the effective filing date of the instant application, development of methods to introduce peptides and proteins into a cell was at a very early stage of development. Therefore, the skilled artisan would not be able to readily deliver a ribosome into a cell without specific guidance from the specification.

Amount of direction provided by the inventor and existence of working examples: The specification contains no mention of delivering ribosomes. Thus, there is no guidance that would suggest that the claimed compositions as disclosed would be capable of delivering a ribosome into any useful location (*i.e.*, into a cell) and no guidance that would enable the skilled artisan to further develop the disclosed compound such that delivery of a ribosome into a cell could be obtained.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not

be able to make an emulsion for delivery of a ribosome into a cell without undue experimentation. Given the art recognized unpredictability of delivering a large protein/nucleic acid complex such as a ribosome into a cell, the skilled artisan would not expect that the disclosed oil-in-water emulsions, which are demonstrated to deliver only nucleic acids into cells, would be capable of delivering a ribosome into a cell. Furthermore, given that the specification is silent with regard to delivering ribosomes into cells, the skilled artisan would not know how to modify the emulsion such that ribosomes into cells. Therefore, making an oil-in-water emulsion for delivering a ribosome as recited in the instant claims would require undue experimentation. Thus, the claims are properly rejected under 35 USC §112, first paragraph as lacking enablement for the full scope of the claimed subject matter.

Conclusion

The claims are free of the art. The claims are directed to an oil-in-water lipid emulsion comprising 2-30% of non-triglyceride oil, 0.01-20% of one or more cationic lipid transfection agents and water to 100%, and a method of making said oil-in-water lipid emulsion comprising preparing an aqueous phase by mixing 0.01-20% of one or more cationic lipid transfection agents with water and emulsifying said aqueous phase with 2-30% of non-triglyceride oil.

The closest art, exemplified by Hartounian *et al.* US Pub. No. 2002/0039596, teaches production of multivesicular liposomes contemplated as useful for delivering nucleic acids, among many other active agents, by providing a water in oil emulsion made from an aqueous phase dispersed in a solvent phase containing amphipathic and neutral lipids (see especially paragraph 0017). Hartounian *et al.* further contemplates squalenes as neutral lipids useful in the

emulsions (paragraph 0027) and amphipathic lipids having a net positive charge (paragraph 0026). However, Hartounian *et al.* does not teach or producing emulsions according to the formulation recited in the instant claims and there is nothing in the prior art that would suggest that an oil-in-water lipid emulsion comprising 2-30% of non-triglyceride oil, 0.01-20% of one or more cationic lipid transfection agents and water to 100% would be particularly desirable. Therefore, the claimed invention, as a whole, would not have been obvious to the skilled artisan.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M Sullivan, Ph.D.
Examiner
Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER